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(54) Title: FUNGICIDE COMPOSITION CONTAINING TEA TREE OIL.

(57) Abstract: A novel fungicidal emulsion is presented. This emulsion comprising tea tree essential oil and a water emulsion wherein the emulsifier is a water solution of a reaction product of a high molecular weight organic fatty acid and an alkali or ammonium compound.

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FUNGICIDE COMPOSITION CONTAINING TEA TREE OIL

FIELD OF THE INVENTION

The present invention generally relates fungicide composition containing teat tree oil (hereinafter TTO) and more specifically to an etheric oil emulsion obtained from the tea tree, especially adapted for the control of wide range of fungal plant pathogens.

BACKGROUND OF THE INVENTION

Increasing intensive agriculture favors the epidemic development of many new and previously unknown plant pests. This development has in turn necessarily led to the use of increasing dosage of chemicals, which negatively affects environmental health. On the other hand, registered pesticides are not always available to control pests effectively and reliably. Therefore, health and environmental considerations dictate the need for alternative method of pest control, which can be promoted as possible strategies for inclusions in an Integrated Pest Management program. This program is a combination of crop protection practice, designed to maintain pests below a designated economic threshold; these practice fall into the categories of chemical; cultural and host-plant resistance.

The control and treatment of plant diseases in green houses and field-grown horticultural corps is a serious problem in agriculture. So far powdering or spraying compositions of mineral source, e.g., sulfur, cuprous hydroxide, calcium polysulfate etc. or compositions based on detergents or oils have been mainly used. However, the use of said compositions is very unsatisfactory as they have many drawbacks.

It has been shown that tea tree oil inhibits certain fungi (See for example Australian Journal of Experimental Agriculture 39:1, 86 -81, 1999). The treatment was satisfactory as it killed the fungi to a large extent, and mainly fungi that attack human, while in plants it caused phytotoxicity to attacked plants.

It was thus desirable to develop a composition adapted to the treatment of a wide range of fungal plant pathogens, e.g., which would not use any of the above known compositions, e.g., mineral oils, detergents and/or fats. However, it may comprise tea tree oil as one of its components. It should be convenient to use and be stable.

SUMMARY OF THE INVENTION

It is thus the core of the invention to provide a cost effective fungicidal emulsion comprising tea tree oil and a water emulsion, wherein the emulsifier is a water solution of a reaction product of a high molecular weight organic fatty acid and an alkali or ammonium compound. Preferably, the emulsion additionally comprising etheric oil. This etheric acid may be selected among lavender oil, pine oil, manuka oil, kanuca oil, eucalyptus oil, bergamot oil, clove oil, lemon oil, lemon grass oil, rosemary oil, geranium oil.

It is in the scope of the present invention wherein the concentration of the tea tree oil is between 0.01% up to 10%, and preferably between 0.1% to 1.5%. It is also in the scope of the present invention wherein the concentration of the tea tree oil is between 0.1% to 1.5%, wherein the concentration of the product is 0.1% to 1% and further wherein the remainder being water.

It is also in the scope of the present invention wherein the alkali and ammonium compounds are selected among sodium, potassium and/or ammonium hydroxides, carbonates, bicarbonates or any mixture thereof. Preferably, the concentration of the additional etheric oils is between 0.01% to 5%.

It is still in the scope of the present invention wherein the acid is selected among; (a) tall oil acids, naftenic acids, rosin acids and any mixture thereof; (b) saturated fatty acid selected among lauric acid, myristic acid, palmitic acid, stearic acid, arachidonic acid, behenic acid, lingoceric acid or any mixture thereof; and, (c) unsaturated fatty acids selected among decenoic acid, dodecenoic acid, palmitoleic acid, oleic acid, linoleic acid, undecelonic acid, sorbic acid, ricinoleic acid or any mixture thereof.

DETAILED DESCRIPTION OF THE INVENTION

The following description is provided, alongside all chapters of the present invention, so as to enable any person skilled in the art to make use of said invention and sets forth the best modes contemplated by the inventor of carrying out this invention. Various modifications, however, will remain apparent to those skilled in the art, since the generic principles of the present invention have been defined specifically to provide fungicide compositions containing tea tree oil (hereinafter 'fungicide composition'), and more specifically to provide an effective emulsion containing etheric components obtained from the tea tree, especially adapted for the control of wide range of fungal plant pathogens.

This fungicide composition is a fungicidal emulsion comprising tea tree oil and a water emulsion; wherein the emulsifier is a water solution of a reaction product of a high molecular weight organic fatty acid and an alkali or ammonium compound.

The term 'tea tree' (i.e., TT) is referring hereinafter to *Melaleuca alternifolia* known in the common name "tea tree." More generally, the term is referring to any of the laurel tree family, unusual variety indigenous to the east coast of New South Wales, Australia.

The term 'tea tree oil' (i.e., TTO) is generally referring hereinafter to any water miscible and water immiscible ingredient of the TT. More specifically, the term TTO is referring to terpinen-4-ol type oils consisting chiefly of terpinenes, cymenes, pinenes, terpeneols, cineole, sesquiterpenes, and sesquiterpene alcohols. The term TTO is also referring to any naturally obtained or chemically synthesized or purified composition comprising terpinen-4-ol oils, 29-45%; γ -terpinene, 10-28%, α -terpinene, 2.7-13%; 1,8-cineole, 4.5-16.5%, and various terpenes, 1-5% selected yet not limited to α -pinene, limonene, p -cymene and terpinolene.

The term 'emulsion' is referring hereinafter to any water in oil (W/O); oil in water (O/W); W/O/W and/or O/W/O phases comprising the TTO inside, outside or at the surface of aggregates, vesicles, micelles, reversed micelles, nano-emulsions, micro-emulsion, liposomes or in any combination thereof.

The term 'emulsifier' is referring hereinafter to any material or molecule provided as a polymer, oligomer or monomer and is nonionic, anionic or cationic detergent and/or surfactant. The emulsifier is preferably comprises of both hypophilic and hydrophilic portions, such as in saturated or non saturated long chain alkyl comprising at least one polar or charged atom.

The terms 'water' and/or 'water solution' are specifically referring hereinafter to water or water solutions, and more generally to any natural or purified, distilled, filtered, de-ionized waters, water suspensions, water-miscible solvents or diluents, water miscible aqueous phase or water-miscible emulsion or any combination thereof.

This fungicide composition consists in a fungicidal emulsion comprising TTO and a water emulsion in which the emulsifier is a water solution of a reaction product of a high molecular weight organic fatty acid and an alkali or ammonium compound.

It is one embodiment of the present invention wherein the aforementioned fungicide composition additionally comprising etheric oils, selected yet not limited to at least one of the group of lavender oil, pine oil, manuka oil, kanuca oil, eucalyptus oil, bergamont oil, clove oil, limonene oil etc.

It is another embodiment of the present invention wherein the aforementioned high molecular weight fatty acid, fatty acids or a mixture of said acids is saturated, unsaturated or comprising a combination of the two, one or all referred hereto in the short term 'high molecular weight fatty acid'.

It is another embodiment of the present invention wherein the aforementioned high molecular weight fatty acid comprising linear or branched alkyl chains of $C > 12$ atoms per molecule. It is in the scope of the present invention wherein those high weight fatty acids are selected in a non-limiting manner from at least one of the following groups:

- a. tall oil acids, naftenic acids, rosin acid or any combination thereof;
- b. saturated fatty acids selected from the group of lauric acid, myristic acid, palmitic acid, stearic acid, arahinoic acid, behenic acid, lingocerinic acid or any combination thereof;

- c. unsaturated fatty acids selected from the group of decenoic acid, dodecenoic acid, palamitinoleic acid, oleic acid, lonoleic acid, undecelenic acid, sorbic acid, recinoleic acid or any combination of thereof.

According to yet another embodiment of the present invention, those acids are treated with alkali hydroxides, carbonates, bicarbonates or any combination thereof to obtain a salt. Additionally or alternatively, the hereto-defined acids are admixed with sodium, potassium or ammonium compounds, e.g., hydroxides, carbonates, bicarbonates or any combination thereof to obtain a salt.

According to yet another embodiment of the present invention, the emulsion comprises from 0.01% to 10%, preferably from 0.1% to 1.5% TTO and from 0.02% to 10%, preferably between 0.1% to 1% of the aforementioned salt, wherein the remainder being water as defined above.

According to yet another embodiment of the present invention, the emulsion additionally comprises of etheric oil. The concentration of said etheric oil is between 0.01% to 5%, preferably 1% to 5%.

According to yet another embodiment of the present invention, the emulsion is prepared by admixing a water solution comprising alkali hydroxide, carbonate or bicarbonate with a liquid solution of organic acid; subsequently admixing a TTO or a TTO-etheric acid mixture. Said admixing step is provided in the manner homogeneous composition is obtained.

Freshly prepared salts solution in water give good emulsification of TTO in a wide concentration range. However, it is possible to use industrially prepared alkali salts of organic acid in powder or in granulated form to dissolve the salt obtained in hot water and to use the received solutions for the emulsification of the TTO.

The TTO containing fungicide composition and especially the fungicide compositions obtained by means of the aforementioned method are characterized with fungicide activity and by significant plants, corps and soil diseases such as those described in table 2 in a non limiting manner:

Table 1 An extractive list of corps pathogens affectively treated by means of the TTO containing fungicide composition according to the present invention.

| Pathogen | Disease | Corp |
|-----------------------------------|------------------------------------|-----------------------------------------------------|
| <i>Oomycetes</i> | Downy mildews and Late blight | Grape, cucurbits, tomato, potato |
| <i>Phytophthora infestans</i> | Late blight | Tomato, potato |
| <i>Plasmopara viticola</i> | Downy mildews | Grape |
| <i>Pseudoperonospora cubensis</i> | Downy mildews | Cucurbits |
| <i>Ascomycetes</i> | Powdery mildews | Grape, cucurbits, tomato, pepper |
| <i>Uncinula necator</i> | | |
| <i>Spaerotheca fuliginea</i> | Powdery mildews | |
| <i>Levillula taurica</i> | | |
| <i>Basidiomycetes</i> | Rust diseases | Roses |
| <i>Tranzschelia discolor</i> | Rust | Prunes, plums, peaches |
| <i>Fungi imperfecti</i> | Alternaria | Various corps |
| <i>Alternaria solani</i> | Early blight | Tomato, potato |
| <i>Alternaria alternata</i> | Leaf and fruit decays and spots | Various corps |
| <i>Aspergillus niger</i> | Decays and spots | Various corps |
| <i>Cladosporium spp.</i> | Leaf spots, decays | Various corps, e.g., tomato and apple |
| <i>Penecillium spp.</i> | Decays | Various corps, e.g., citrus |
| <i>Penecillium italicum</i> | Decays | |
| <i>Penecillium digitatum</i> | Decays | |
| <i>Botrytis cinerea</i> | Fruit rots and decays | Various corps, e.g., vegetables flowers, grapes. |
| <i>Stemphillium spp.</i> | Leaf spots | Various corps |
| <i>Trichoderma</i> | | Various corps |
| <i>Fusarium</i> | Decays, rots | Various corps |
| <i>Rhizoctmia spp.</i> | Decays, rots | Various corps |
| <i>Helmintho spp.</i> | Decays, rots | Potato |

The TTO containing fungicide composition according to the present invention is useful for treating the pathogens located in the flowers, fruits, leaves, roots, tubers, bulbs, etc.

In order to understand the invention and to see how it may be implemented in practice, a plurality of preferred embodiments will now be described, by way of non-limiting example only, with reference to the following examples, wherein all percentages are denoted for weight percents.

Example 1

300 g of naftenic acid are mixed with 160 g of 1 25% solution of NaOH in water for 60 minutes at 70°C. 316 g TTO is admixed to the reaction product obtained by a means of a contentions stirring until full homogenization is obtained. From the composition obtained, which contains 50% TTO, a stable TTO O/W emulsion is prepared by contentiously admixing of water, in the manner an emulsion comprising from 0.001% to 49.9% of oil.

Example 2

Into a 25% water solution of 300 g KHCO_3 , some 400 g of melted stearic acid is admixed at 75°C for 30 min. Subsequently, a mixture of 500 g of TTO and 200 g of lavender oil is admixed to the alkali admixture until a full homogenization is obtained. From the composition obtained, a stable TTO O/W emulsion comprising from 0.001% to 49.9% of etheric oil is obtained.

Example 3

30 g of Na_2CO_3 were dissolved in 100 g of water at 50°C for 30 min. This solution was admixed with 120 g of tall oil acid, comprising 25% of rosin acid for additional 30 min. The obtained mixture was dissolved in 500 g of TTO until a homogenized solution is obtained. A plurality of stable TTO-containing emulsions was subsequently obtained.

Example 4

280 g of oleic acid was admixed with 85 g of a 20% ammonia solution at 60°C. 400 g of TTO was admixed until a homogenized solution was obtained.

Example 5

30 g of Na_2CO_3 were dissolved in 100 g of water at 50°C for 30 min. This solution was admixed with 120 g of tall oil acid, comprising 25% of rosin acid for additional 30 min. The obtained mixture was dissolved in 250 g of TTO and 250g of pine oil until a homogenized solution is obtained. A plurality of stable TTO-containing emulsions was subsequently obtained.

Example 6

The stable TTO-containing emulsions obtained in examples 1-5 were proved useful for treating the corps against pathogens selected from *Oomycetes*; *Phytophthora infestans*; *Plasmopara viticola*; *Pseudoperonospora cubensis*; *Ascomycetes*; *Uncinula necator*; *Spaerotheca fuliginea*; *Levillula taurica*; *Basidiomycetes*; *Tranzschelia discolor*; *Fungi imperfecti*; *Alternaria solani*; *Alternaria alternata*; *Aspergillus niger*; *Cladosporium spp.*; *Penecillium spp.* ; *Penecillium italicum*; *Penecillium digitatum*; *Botrytis cinerea*; *Stemphillium spp.* ; *Trichoderma*; *Fusarium*; *Rhizoctomia spp.*, and *Helmintho spp.*

The stable TTO-containing emulsions obtained in examples 1-5 were proved useful for *in vitro* inhibiting spore germination and/or mycelia growth of the fungi. More specifically, the fungicide composition was proved useful prophylactic and local activity in intact plants and detached leaves. Foliar applications of the TTO compositions to field-grown grapevines and melons inhibit downy and powdery mildews development, respectively. The inhibitory effectiveness of TTO compositions makes it well suited for integration into control programs targeted against various diseases in agricultural organic-grown corps and as a replacement of sulfur and/or cupper containing pesticides.

The experiments were performed by one of the following methods:

Spore germination test of downy mildews late blight, *Alternata* and rust pathogens

Sporangial suspensions were mixed with various concentrations of TTO, which ranges from 0 to about 1%, and 0.1 mL droplets were transferred to depression glass slides (4 slides per each concentration). Slides were incubated in moist Petri dishes at 20°C in darkness for about 8 hours. The percentage of sporangia releasing zoospores and of zoospores producing germ tubes were counted under the microscope.

Effect of germination of conidia of powdery mildews pathogens

TTO was dissolved and admixed with sterile distilled water to give a stock solution of a known concentration. TTO was admixed with pre-autoclaved 1% water agar to give final concentrations of 0%, 0.001%, 0.01%, 0.1% and 1%. Conidia were shaken onto glass slides previously coated with water agar containing TTO. Slides were placed in Petri dishes containing wet filter paper and kept in the dark at 20°C for about 16 hours. The number of germinated conidia was counted under a microscope.

***In vitro* activity of mycelia growth of fungi**

3 mm diameter agar disks bearing the tested fungus were taken from freshly growing colony on potato dextrose agar, 39 g of Difco in 1 liter of distilled water, and placed on freshly amended with various concentrations of TTO in 9 cm diameter Petri dishes. Plates were incubated at 25°C for about 6 days in the dark, and the colony diameter was recorded every two days. Three Petri dishes, each containing three inoculum disks, were used for each treatment concentration. Experimented were carried on in duplicates.

***In vivo (in planta)* experiments**

Plants were sprayed with TTO at various concentrations ranges from 0 to 2% on both surfaces, and 24 hours later were inoculated on the lower surface with sporangial suspension of *Plasmopara viticola* (grape downy mildew). The lower surface of each of six to eight attached leaves on each of six plants of each treatment was uniformly sprayed with 2 mL of a sporangial suspension of 4×10^4 sporangia per mL, delivered from a glass chromatography sprayer. After inoculation, plants were covered with plastic gages, lightly sprayed on the inside with water, and were incubated at 19°C for about 20 hours in

darkness. The plants were then uncovered and kept in a growth chamber for disease development. 9 days after inoculation, disease developed on each leaf of treated plant was evaluated. In some cases, plants were lightly sprayed with water, covered with plastic bags and incubated at 19°C for 24 hours in darkness, to induce sporulation to determine sporangial production. Leaves are bleached and the percent leaf area covered with sporangiophores and sporangia of *P. viticula* were visually estimated and recorded. The number of sporangia produced per square centimeter of leaf tissue was calculated as described above for leaf disks.

Powdery mildew inoculations

Conidia were shaken onto leaves previously treated with TTO or with water. Plants were incubated in growth-room and percentage of leaf area covered with powdery mildew was assessed.

Experiments were also performed to evaluate the biological activity of the compositions according to the present invention against fungal pathogens. The experiments were performed with the emulsion of the following composition: oleic acid, 150g; sodium hydroxide, 20g; TTO, 270 g, and water, 100 mL.

Example 7

The controlling effect of the TTO-containing emulsion on powdery mildew by *Spaerotheca fuliginea* in field-grown melon plants was studied:

Table 2 The inhibition of infected leaf area as to a control as function of treatment by TTO-containing emulsions. Analysis was studied at the upper side of the leaf.

| Treatment and Concentration (%) | % Inhibition of infected least area as to a control |
|---------------------------------|-----------------------------------------------------|
| Control | --- |
| 0.25 | 50.0 |
| 0.50 | 75.5 |
| 1.00 | 84.5 |

Example 8

The effect of TTO-containing emulsions on the *in vivo* germination of grape powdery mildew pathogens was studied:

Table 3 The inhibition of conidial germination as a function of TTO concentration:

| Treatment and Concentration (%) | % Inhibition of conidial germination |
|---------------------------------|--------------------------------------|
| Control | --- |
| 0.1 | 100 |
| 0.01 | 96 |
| 0.001 | 63 |

Example 9

The effect of TTO-containing emulsions on grape downy mildew was studied:

Table 4 The inhibition of infected leaf area as a function of TTO concentration:

| Treatment and Concentration (%) | % Inhibition of infected leaf area |
|---------------------------------|------------------------------------|
| Control | --- |
| 1.0 | 100 |
| 0.5 | 100 |
| 0.25 | 99 |

Example 10

The effect of TTO-containing emulsions on mycelia growth of *Alternaria alternaria* was studied:

Table 5 The inhibition of *A. alternaria* as a function of TTO concentration:

| Treatment and Concentration (%) | % Inhibition of infected leaf area |
|---------------------------------|------------------------------------|
| Control | --- |
| 0.5 | 100 |
| 0.25 | 68 |
| 0.10 | 30 |

It is acknowledged in this respect that TTO-containing compositions are useful fungicides. It controls *S. fuliginea* in field-grown melon plants, inhibits germination of the grape powder mildew fungus *U. necator* in which a concentration of 0.1% completely inhibits germination at concentrations between 0.01% to 0.001% it provided 96% and 63 inhibition, respectively. It was also proven effective in controlling foliar disease on leaves of potted plants, for example by spraying of 0.25% of TTO, a complete inhibition of grape downy mildew was obtained. Lastly, it was also prove effective in inhibiting mycelia growth of various fungi.

CLAIMS

1. A fungicidal emulsion comprising tea tree oil and a water emulsion wherein the emulsifier is a water solution of a reaction product of a high molecular weight organic fatty acid and an alkali or ammonium compound.
2. The emulsion according to claim 1, additionally comprising etheric oil.
3. The emulsion according to claim 2, wherein additional etheric oil is selected among lavender oil, pine oil, manuka oil, kanuka oil, eucalyptus oil, bergamot oil, clove oil, lemon oil, lemon grass oil, rosemary oil, geranium oil.
4. The emulsion according to any of claims 1 –3, wherein the concentration of the tea tree oil is between 0.01% up to 10%.
5. The emulsion according to claim 4, wherein the concentration of the tea tree oil is between 0.1% to 1.5%.
6. The emulsion according to claims 4 or 5, wherein the concentration of the tea tree oil is between 0.1% to 1.5%, wherein the concentration of the product is 0.1% to 1% and further wherein the remainder being water.
7. The emulsion according to any of claims 1 to 6, wherein the alkali and ammonium compounds are selected among sodium, potassium and/or ammonium hydroxides, carbonates, bicarbonates or any mixture thereof.
8. The emulsion according to any of claims 2 to 7, wherein the concentration of the additional etheric oils is between 0.01% to 5%.
9. The emulsion according to any of claims 1 to 8, wherein the acid is selected among;
 - a. tall oil acids, naftenic acids, rosin acids and any mixture thereof,

- b. saturated fatty acid selected among lauric acid, myristic acid, palmitic acid, stearic acid, arachidonic acid, behenic acid, lignoceric acid or any mixture thereof, and,
 - c. unsaturated fatty acids selected among decenoic acid, dodecenoic acid, palmitoleic acid, oleic acid, linoleic acid, undecylenic acid, sorbic acid, ricinoleic acid or any mixture thereof.
10. The emulsion according to claim 1, substantially as herein described with reference to the examples.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 03/00717

| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A01N65/00 | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A01N | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, PAJ, CHEM ABS Data, WPI Data | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | US 5 449 517 A (FITZJARRELL EDWIN A) 12 September 1995 (1995-09-12) claim 1 column 2, line 2-5 column 2, line 44 - line 46 --- | 1-10 |
| A | WO 02 21926 A (BARRIER BIOTECH LTD ;MORRIS SANDRA (GB); RYAN ROBERT EUGENE (GB)) 21 March 2002 (2002-03-21) page 4, line 14-20 page 5, line 22 - line 32 page 15 --- -/-- | 1-10 |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. | | |
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| Date of the actual completion of the international search 1 December 2003 | | Date of mailing of the international search report 16/12/2003 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer Decorte, D |

INTERNATIONAL SEARCH REPORT

Intern cation No
PCT/IL 03/00717

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A | <p>PATENT ABSTRACTS OF JAPAN vol. 016, no. 213 (C-0942), 20 May 1992 (1992-05-20) & JP 04 041407 A (HIROYUKI KOIKE; OTHERS: 01), 12 February 1992 (1992-02-12) abstract</p> | |
| A | <p>PATENT ABSTRACTS OF JAPAN vol. 014, no. 390 (C-0751), 23 August 1990 (1990-08-23) & JP 02 145502 A (UBE IND LTD), 5 June 1990 (1990-06-05) abstract</p> | |
| A | <p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MARKHAM, JULIE L.: "Biological activity of tea tree oil" retrieved from STN Database accession no. 131:120639 XP002263358 abstract & MEDICINAL AND AROMATIC PLANTS—INDUSTRIAL PROFILES (1999), 9(TEA TREE), 169-190 ,</p> | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati ation No
PCT/IL 03/00717

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---|---------------------|----------------------------------------------------------------|------------------------------------------------------|
| US 5449517 | A | 12-09-1995 | NONE | |
| WO 0221926 | A | 21-03-2002 | AU 8608001 A CA 2421935 A1 WO 0221926 A2 GB 2369052 A | 26-03-2002 21-03-2002 21-03-2002 22-05-2002 |
| JP 04041407 | A | 12-02-1992 | NONE | |
| JP 02145502 | A | 05-06-1990 | NONE | |